PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

CORRECTED VERSION

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Applicant's or agent's file reference PRD2061-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/006280	International filing date *(day/month/year)* 10.06.2004	Priority date *(day/month/year)* 19.06.2003

International Patent Classification (IPC) or national classification and IPC
C07D405/12, A61K31/445, A61P1/00

Applicant
JANSSEN PHARMACEUTICA N.V.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.2005	27.09.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006280

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-44 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9

because:

☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-8,10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Reference is made to the following documents :

D1: WO00/37461
D2: WO00/15636
D3: WO99/02156
D4: ES 2 103675

The present application deals with aminosulfonyl or dicarbonylamine substituted 4-(aminomethyl)-piperidine benzamide derivatives as 5HT4-antagonists for the treatment of gastrointestinal disorders.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The unique common concept linking together the subject-matters of claims 1-10 is the presence of a 4-benzamidomethylpiperidine substituted in 1-position by an alkyl chain itself substituted by a group containing a nitrogen atom (unique common element between aminosulfonyl ((b-1) to (b-3) and (b-5) to (b-7)) and dicarbonylamine (b-4)), said compounds being useful as 5-HT4 antagonists in the treatment of gastrointestinal diseases. Such a structural feature is already disclosed in WO00/37461 (see compounds 17 and 47 wherein L is Alk-(N-containing)group) for compounds which exhibit the same activity. Since the common feature is not novel, it cannot represent the single inventive concept which could have linked the different claimed subject-matters together.

The technical relationship between the different subject-matters of claims 1-10 required by rules 13.1 PCT is lacking and the requirement for unity of invention referred to in Article 17.3(a) PCT is not fulfilled.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Document D1 discloses 1-substituted 4-(benzamidomethyl)-piperidine derivatives as 5HT4-antagonists useful in the treatment of gastrointestinal disorders. Formula (I) of D1 differs from the present claimed subject-matter when L is (b-1) due to the inversion of the amino (NH) and the sulfonyl (SO_2) functions, i.e. D1 discloses L=-Alk-NH-SO_2-Alk whereas the present application deals with L=-Alk-SO_2-NH-Alk. Formula (I) of D1 differs also from the present claimed subject-matter when L is (b-2) due to the presence of an alkyl group on the amino (X according to the present application represents -NAlk-), i.e. D1 discloses L=-Alk-NH-SO_2-Alk whereas the present application deals with L=-Alk-NAlk-SO_2-Alk. Claims 1-10 can be considered novel with regard to document D1 of the prior art (Article 33(2) PCT).

   Document D2 describes 1-substituted 4-(benzodioxineamidomethyl)-piperidine derivatives as 5HT4-antagonists useful in the treatment of gastrointestinal disorders. According to formula (I) of D2, the piperidine ring is disubstituted and may not carry a further oxygen linked substituent. The compounds of D2 differ from the present claimed invention due to the absence of this substituent. Novelty is established with regard to document D2 (Article 33(2) PCT).

   Document D3 reveals 1-substituted 4-(4-aminobenzamidomethyl)-piperidine derivatives with gastric emptying activity. According to formula (I) of D3, the phenyl ring is substituted in 4-position by an amine group. Since the substituent at this position according to the present invention (R^3) may not represent NH_2, novelty of claims 1-10 is also established with regard to document D3 (Article 33(2) PCT).

   Document D4 deals with 1-substituted 4-hydroxy-4-(4-aminobenzamidomethyl) piperidine as 5HT4-antagonists for the treatment of gastrointestinal disorders. According

to D4, the substituent in 1-position of the piperidine may not contain an aminosulfonyl or a dicarbonylamine group as claimed in the present invention. Furthermore, the compounds of D4 are substituted in 4-position of the phenyl ring by an amine group (see definition of R^3 according to the present invention). Novelty of claims 1-10 is also established with regard to document D4 (Article 33(2) PCT).

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-10 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as the closest prior art to the subject-matter of claims 1-10, and discloses 4-(benzamidomethyl)-piperidine derivatives with 5HT4-antagonist activity.

The problem to be solved by the present invention may therefore be regarded as the provision of further 4-(benzamidomethyl)-piperidine derivatives with 5HT4-antagonist activity for use in the treatment of gastrointestinal disorders.

The difference between D1 and the present application lies with the inversion of the sulfonyl and the amine functions (b-1) or the presence of an alkyl group on the amine (b-2) (see point 1). According to D1, alkyl and hydrogen atom are considered to be bioisosters (see definitions of -R1-R2-, R3, R4, etc.). This equivalence is also acknowledged in the application itself (see especially definition of R6). Thus, the introduction of an alkyl group on the amino part of L=-Alk-NH-SO_2-Alk known from D1 appears to be an obvious alternative for the skilled person.

The inversion of the sulfonyl and the amine functions (sulfonylamino instead of aminosulfonyl) appears also to lies within the knowledge of the skilled person. As can be seen from D1, the L moiety can undergo great variations without modification of the biological activity. It is clear from the definition of X according to D1 that NR8 and SO2 are bioisosters which can be exchanged while the biological activity is retained. Furthermore, the application itself considers these alternatives as equivalent (see definition of (b-1) and (b-2)). Therefore, the use of an aminosulfonyl instead of a sulfonylamino is considered to fall within the competence of the skilled person.

Hence, no inventive step is present in the subject-matter of claim 1 (Article 33(3) PCT).

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 7-10, which therefore are also considered not inventive.

Dependent claims 2-6 reveals slight constructional changes with regard to the size of the whole molecule which come within the scope of the customary practice followed by persons skilled in the art. Consequently, the subject-matter of claims 2-6 also lacks an inventive step (Article 33(3) PCT).

3. For the assessment of the present claim 9 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.